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Associations of recreational and non-recreational physical activity with coronary artery calcium density vs. volume and cardiovascular disease events: the Multi-Ethnic Study of Atherosclerosis.

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Authors

Thomas, Isac C
Takemoto, Michelle L
Forbang, Nketi I
et al.

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Title: Associations of Recreational and Non-Recreational Physical Activity with Coronary Artery Calcium Density Versus Volume: The Multi-Ethnic Study of Atherosclerosis

Short title: Thomas, Physical Activity and CAC Composition

Authors:
Isac C. Thomas MD, MPH [a]
Matthew A. Allison, MD, MPH [b]
Matthew J. Budoff, MD [c]
Michael H. Criqui, MD, MPH [b]
Nketi I. Forbang, MD, MPH [b]
Britta A. Larsen, PhD [b]
Robyn L. McClelland, PhD [d]
Erin D. Michos, MD, MHS [e]
Michelle L. Takemoto, PhD [b]

Affiliations:
[a] Division of Cardiovascular Medicine, Department of Medicine, University of California San Diego, La Jolla, California
[b] Division of Preventive Medicine, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, California
[c] Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-University of California Los Angeles Medical Center, Torrance, California
[d] Department of Biostatistics, University of Washington, Seattle, Washington
[e] Division of Cardiology, Johns Hopkins School of Medicine, Baltimore, Maryland

Address for Correspondence:
Isac C. Thomas, MD, MPH
Division of Cardiovascular Medicine
University of California, San Diego
9452 Medical Center Drive
La Jolla, CA 92037-7411
Tel: 858-246-2971, Fax: 858-657-1828
Email: icthomas@ucsd.edu

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Abstract

Background: The beneficial effects of physical activity on cardiovascular disease (CVD) risk are well known. However, several studies have suggested that high-end physical activity (PA) may have deleterious associations with certain markers of subclinical CVD, including coronary artery calcification (CAC). The effect of PA on the composition of CAC is poorly understood.

Methods and Results: We evaluated the associations of self-reported PA with the density and volume components of CAC in 3,398 participants of the Multi-Ethnic Study of Atherosclerosis. After adjusting for demographic variables and CVD risk factors, the highest quintile of recreational physical activity was associated with 0.06 (0.01, 0.11) units greater average CAC density, and had no association with total CAC volume. In contrast, the highest quintile of non-recreational physical activity was associated with 0.09 (0.02, 0.15) units lower average CAC density and 0.17 (0.03, 0.30) log-units greater total CAC volume. Recreational and non-recreational PA were among the strongest modifiable CVD risk factor correlates of CAC density and volume.

Conclusions: As higher CAC density is protective for CVD events, high levels of recreational PA appear to be associated with a more favorable composition of CAC, and non-recreational PA a less favorable composition of CAC, among individuals with prevalent CAC.

Introduction

The benefits of physical activity (PA) on the prevention of cardiovascular disease (CVD) events are well established and promoted broadly in cardiovascular health guidelines.[1-5] However, several studies have suggested that very high levels of PA may be associated with subclinical markers of cardiovascular injury.[6-10] For instance, a recent study evaluating coronary artery atherosclerosis detected by cardiac computed tomography (CT) found a greater prevalence of atherosclerotic plaque among endurance athletes compared to controls.[10] Interestingly, these plaques tended to be predominantly calcified, compared to mostly mixed and non-calcified plaques found among controls. The investigators posited that the calcific nature of these plaques may be reflective of enhanced plaque stability resulting from high-end PA.

The effects of high levels of PA on CAC density are unknown. In the Multi-Ethnic Study of Atherosclerosis (MESA), a higher density of CAC was found to substantially mitigate the risk of incident CVD that was otherwise engendered by the presence of calcified atherosclerosis.[11] The apparently protective association of high CAC density with incident CVD events was similarly posited to be reflective of a potential association between CAC density and enhanced plaque stability.

With this background, we evaluated the associations of self-reported PA with levels of CAC density and volume among a cohort of community-dwelling individuals without baseline clinical CVD. We sought to evaluate if levels of PA have an independent association with the density and volume components of CAC, thus providing insight into the effects of physical activity on the natural history of coronary atherosclerosis.

Methods

Study Participants

We evaluated participants of the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective, population-based cohort study that was performed at six centers across the Unites States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN) and included four race/ethnic groups (Non-Hispanic White, African-American, Hispanic, and Chinese). Institutional Review Boards at each participating center approved the study, and all participants provided written informed consent. Details regarding the study design, recruitment methods, examination components, and data collection have been reported.[12] From 2000-02, a total of 6,814 men and women aged 45-84 years and free of clinical CVD at recruitment completed physical activity questionnaires, detailed medical and social histories, and anthropometric, laboratory and imaging studies including cardiac CT scans for CAC.

Physical Activity

The MESA Typical Week Physical Activity Survey was used to assess the time spent and frequency of various physical activities during a typical week in the past month. A detailed description of the survey has been previously reported.[13] It was comprised of items that encompassed several forms of physical activity, such as work, volunteer, and task-oriented activities as well as activities of intentional exercise and recreation (walking for exercise, sports/dancing, and conditioning). Each form of activity was differentiated by level of intensity (light, moderate, or heavy), where applicable. Respondents reported the average number of days per week and time per day in minutes engaged in each activity, and the product of these two values was multiplied by the metabolic equivalent (MET) level, producing a value of MET-minutes per week for each activity.

For this study, we evaluated two derived variables: recreational PA and non-recreational PA. We defined recreational PA as the following intentional exercise activities typically recommended by PA guidelines: walking exercise, dance, team sports, dual sports, individual exercise activities, and conditioning. Non-recreational PA were remaining items in the survey: household chores, yard work, care of others, walking for transportation, work, and volunteer activities. In line with prior studies reflecting PA guidelines, we included only moderate (3-6 METs) and vigorous (6+ METs) activities.

Coronary Artery Calcium Scores

CAC was assessed via non-contrast, electrocardiogram-gated cardiac computed tomography (CT). Details regarding CT scanning protocols and CAC measurements have been reported previously.[14] An electron-beam CT scanner was used in Chicago, Los Angeles, and New York field centers and a four-slice multi-detector CT system was used in Baltimore, Forsyth County and St. Paul field centers. The nominal slice thickness was 3.0 mm for electron-beam CT and 2.5 mm for four-detector row CT. Certified technologists scanned all participants over phantoms of known physical calcium concentration, and all studies were read at the Los Angeles Biomedical Research Institute at Harbor-UCLA in Torrance, CA.

Calcified plaque within the coronary arteries was identified as attenuation greater than 130 Hounsfield units (HU) with a minimum size of 5.5 mm^3 (electron beam CT) or 4.6 mm^3 (multi-detector CT). The Agatston score was computed by multiplying individual calcified lesion areas by a density factor of 1, 2, 3, or 4, corresponding to the maximum attenuation within each lesion (130-199 HU=1, 200-299 HU=2, 300-399 HU=3, 400+ HU=4).[15] The Agatston scores for each calcified lesion were then summed to produce the total Agatston score. The volume score was computed by summing the products of all calcified lesion areas (mm^2) and multiplying by the CT scan slice thickness. CAC density scores were calculated using the method previously described in the MESA, according to the formula: density score = Agatston score * CT slice thickness / volume score.[11] The density

score is a unitless value that reflects the average density factor of all calcified lesions.

Covariates

Medical history including medication use, socioeconomic history, and laboratory data were collected during the baseline examination of the cohort. Age, gender, race/ethnicity, medication use, annual household income, and level of education level were obtained by self-administered questionnaire. Resting blood pressure was measured three times in the seated position, and the average of the 2nd and 3rd readings was recorded. Total and high-density lipoprotein cholesterol (HDL-C) were measured from blood samples obtained after a 12-hour fast. Smoking status was classified as current, former, or never, with current defined as having smoked a cigarette in the last 30 days. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL or use of hypoglycemic medications.

Statistical Analysis

Recreational and non-recreational PA levels were stratified into quintiles, and descriptive statistics were used to evaluate variation in clinical characteristics across quintiles. ANCOVA was used to calculate adjusted CAC volume and CAC density for each quintile of recreational and non-recreational PA. Multiple linear regression was used to evaluate the independent associations of recreational and non-recreational PA with CAC volume and density, in hierarchical models as follows:

Model 1: recreational PA quintile, non-recreational PA quintile, CAC volume, CAC density, age, sex, race/ethnicity, annual income, level of education

Model 2: Model 1 + CVD risk factors (systolic blood pressure, hypertension medication, total cholesterol, HDL cholesterol, statin medication, cigarette smoking status, pack-years of cigarette smoking, diabetes mellitus, and body mass index)

CAC density scores are only available for participants with detectable CAC. Thus, only participants with prevalent CAC (i.e. CAC volume > 0) were included (n=3,398, 49.9% of total sample). Five participants did not complete the physical activity questionnaire, leaving a final analytical sample of 3,393 participants. CAC volume was natural log transformed to adjust for skewness. Missing covariates (<1% of sample) were imputed using sample means. Analyses were performed using IBM SPSS Statistics (Version 22.0, Armonk, NY: IMB Corp.). A p-value of <0.05 was considered statistically significant.

Results

The mean age of the total sample was 66.3 (±9.5) years, 57.8% were male, and the race/ethnicity distribution was 44.0% Caucasian, 24.1% African American, 20% Hispanic, and 11.9% Chinese-American. Tables 1 and 2 display characteristics of sample participants stratified by quintile of

recreational and non-recreational PA, respectively. Higher levels of recreational PA were associated with a lower proportion of female participants (down to 33% in quintile 5) and a generally more favorable CVD risk factor profile. Participants in quintile 5 of recreational PA also reported the highest amount of non-recreational PA (median 3,315 MET-min/week). Higher quintiles of non-recreational PA were associated with a lower age and lower proportion of female participants, and tended to have a higher proportion of current or former smokers (60% in quintile 5) and higher BMI levels (28.7 kg/m^2 in quintile 5). Participants in quintile 5 of non-recreational PA also reported the highest amount of recreational PA (median 1,260 MET-min/week). When evaluated as continuous variables, amounts of recreational and non-recreational PA were modestly correlated with each other (Pearson correlation coefficient=0.22).

Figure 1 shows mean CAC density scores (panel A) and mean CAC volume scores (panel B) across quintiles of recreational and non-recreational PA, mutually-adjusted for quintile of recreational and non-recreational PA, as well as CAC density and volume. CAC density varied minimally across quintiles 1-4 of recreational PA, with a modest increase seen in quintile 5 to 2.74 (2.70, 2.79). Mean CAC density trended consistently downward across quintiles of non-recreational PA, to a low of 2.61 (2.57, 2.65) in quintile 5. Mean CAC volume did not have a consistent trend across quintiles of recreational or non-recreational PA, with peak scores in quintile 3 of recreational PA (4.49 [4.39, 4.59] ln-units) and quintile 4 of non-recreational PA (4.46 [4.36, 4.56] ln-units).

Table 3 displays adjusted regression coefficients for quintiles of recreational and non-recreational PA. With quintile 1 serving as the reference, quintiles 2 through 4 of recreational PA had no association with CAC density, but in quintile 5 a significant positive association was observed. Given this apparent threshold association, we collapsed quintiles 1-4 into one reference category for analysis of recreational PA. With adjustment for demographic and socioeconomic variables (Model 1), recreational PA was associated with higher CAC density in quintile 5 (B=0.07 [0.01, 0.12]). With further adjustment for CVD risk factors (Model 2), this association was attenuated slightly but remained significant (Model 2, B=0.06 [0.01, 0.11]). In contrast, quintile 5 of recreational PA was not significantly associated with CAC volume, but showed a trend toward lower CAC volume (B=-0.09 [-0.19, 0.02]).

Non-recreational PA displayed a stepwise trend across quintiles toward a lower CAC density score and a higher CAC volume score, with quintile 5 meeting statistical significance for CAC density (B=-0.08 [-0.14, -0.02]), and near-significance for CAC volume (B=0.13 [-0.01, 0.27] ln-units) in Model 1. Further adjustment for Model 2 variables strengthened the associations with CAC density (quintile 5 B=-0.09 [-0.15, -0.02]) and CAC volume (quintile 5 B=0.17 [0.03, 0.30]).

Figure 2 plots the regression coefficients for modifiable CVD risk factors included in Model 2, with coefficients for continuous variables

reflecting one standard deviation increment. Among these risk factors, quintile 5 of recreational PA had the largest positive association with CAC density, and quintile 5 or non-recreational PA had the largest inverse association. The association of quintile 5 of non-recreational PA with CAC volume was similar in magnitude to current cigarette use and statin medication use.

No statistically-significant interactions were observed by sex or race/ethnicity.

Discussion

In a multi-ethnic, population-based sample of individuals with prevalent CAC, we found that the highest level of recreational PA was associated with a higher average density of CAC. Furthermore, after adjusting for CAC density and non-recreational PA, recreational PA at any level had no association with the volume of CAC. These associations were minimally impacted by adjustment for several CVD risk factors, suggesting a direct association between recreational PA and a more favorable composition of CAC. We also found that recreational PA was among the strongest independent correlates of CAC density among modifiable CVD risk factors. As CAC density is inversely associated with CVD events, these findings align with evidence supporting the benefits of recreational PA on CVD risk.

Prior studies among athletes have demonstrated an association between high levels of physical activity and CAC. Mergani et al. showed that CAC prevalence was higher among male endurance athletes compared to controls (44% vs. 22%), and Agatston CAC scores were higher among those with prevalent CAC.[10] They went on to evaluate all atherosclerotic plaques (i.e. calcified, non-calcified, and mixed morphology) using contrast-enhanced studies, and found that while they were more numerous in endurance athletes, the plaques were more calcified compared to controls. While we were unable to evaluate non-calcified coronary plaque given the absence of contrast–enhancement in our study, the higher CAC density scores we observed at the highest level of recreational PA may be reflective of overall plaque composition being more calcified. Aengevaeren et al. evaluated CAC among male athletes and found no significant difference in CAC density scores across levels of lifelong exercise.[9] However, the investigators appear to have not adjusted for CAC volume or non-recreational PA, two potentially confounding variables that may obscure the association between exercise and CAC density.

The effects of non-recreational PA on coronary plaque characteristics and CAC are poorly understood. We found that non-recreational PA was *inversely* associated with CAC density and positively associated with CAC volume, unfavorable associations on par with those of several modifiable CVD risk factors. Several studies have suggested an association between non-recreational PA and a higher risk of CVD events,[16-18] yet recently published findings from the multinational Prospective Urban Rural Epidemiologic study show that non-recreational PA has a strong protective

association with mortality and major CVD events. The deleterious associations of non-recreational PA with CAC composition that we observed may reflect unmeasured confounding by socioeconomic status and use of medical therapies. For instance, those in the highest quintile of non-recreational PA had the lowest annual income and least use of statins.

Our study has several strengths. We evaluated a large, multi-ethnic, community-dwelling sample free of clinical cardiovascular disease, enhancing the generalizability of these findings. However, our study also has limitations. Physical activity was assessed via self-report rather than objective measurement. Given the cross-sectional nature of this analysis, causal relationships cannot be determined. The CAC density score is derived from the Agatston score, and is thus subject to inherent imprecisions that may attenuate the magnitude of association between PA and CAC density. The Agatston score assigns density scores based on a four-point ordinal scale, with the peak density of each lesion determining the density score for the entire lesion, and all densities greater than 400 Hounsfield units arbitrarily capped at a density score of four. Thus, heterogeneous CAC lesions of high peak but primarily low density plaque are misclassified as high density lesions, and very high density lesions are inaccurately assigned lower density scores.

In conclusion, among individuals with prevalent CAC, high levels of recreational PA are associated with higher CAC density, and recreational PA at any level is not associated with CAC volume, findings that may explain the higher levels of calcified coronary atherosclerosis seen among athletes with favorable CVD risk factor profiles. In contrast, non-recreational PA is associated with CAC of lower density and higher volume. Although the associations were small, these PA variables are among the strongest modifiable risk factor correlates of CAC density and volume. Our findings also support evaluating self-reported recreational and non-recreational PA as distinct variables that may have disparate associations with subclinical cardiovascular disease in epidemiological studies.

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Table 1: Sample Characteristics Stratified by Quintile of Recreational Physical Activity

Recreational PA Quintile	1	2	3	4	5	*p-value*
N (3,393 participants)	775	685	625	654	654	
Recreational PA (MET-min/week)	0 [0, 0]	368 [210, 525]	990 [795, 1140]	1852 [1530, 2175]	3960 [3120, 5706]	<0.01
Non-Recreational PA (MET-min/week)	1995 [555, 5010]	1905 [810, 3945]	2160 [900, 4455]	2340 [1118, 2003]	3315 [1560, 7080]	<0.01
Age (years)	66.6 (9.6)	66.3 (9.9)	66.9 (9.7)	66.2 (9.2)	65.8 (9.2)	0.30
Female	48%	49%	41%	38%	33%	<0.01
Race/ethnicity						<0.01
White	35%	44%	46%	48%	48%	
Chinese	11%	12%	14%	15%	8%	
African-American	27%	24%	22%	23%	24%	
Hispanic	27%	20%	18%	14%	19%	
Level of education						<0.01
< High School	29%	22%	17%	12%	11%	
High School+	39%	36%	35%	33%	33%	
College+	32%	42%	48%	55%	56%	
Annual income						<0.01
<$50,000	75%	65%	62%	58%	55%	
$50,000-$99,999	20%	25%	25%	24%	28%	
$100,000+	5%	10%	13%	18%	17%	
Systolic blood pressure (mm Hg)	133 (23)	132 (22)	130 (21)	131 (21)	129 (20)	0.01
Hypertension medication	48%	49%	47%	44%	41%	0.02
Total cholesterol (mg/dL)	194 (37)	196 (37)	194 (35)	194 (36)	195 (38)	0.76
HDL cholesterol (mg/dL)	48 (14)	50 (15)	49 (14)	50 (15)	50 (15)	0.03
Statin medication	19%	22%	19%	21%	20%	0.55
Cigarette smoking status						<0.01
Never	43%	48%	48%	43%	42%	
Former	41%	39%	41%	46%	46%	
Current	17%	14%	11%	11%	12%	
Pack-years of cigarette smoking	3.5 [0, 27]	0.25 [0, 21]	0.23 [0, 20]	2.0 [0, 22]	2.4 [0, 17]	<0.01
Diabetes mellitus	20%	17%	17%	14%	12%	<0.01
Body mass index (kg)/(m^2)	29.5 (6.1)	28.9 (5.6)	28.0 (4.8)	27.6 (4.8)	27.6 (4.5)	<0.01

Values presented are means (standard deviations) or medians [interquartile range]. CAC=coronary artery calcium, HDL=high density lipoprotein, MET=metabolic equivalent of task, PA=physical activity.

Table 2: Sample Characteristics Stratified by Level of Non-Recreational Physical Activity

Non-Recreational PA Quintile	1	2	3	4	5	*p-value*
N (3,393 participants)	678	685	675	679	676	
Non-Recreational PA (MET-min/week)	315 [105, 480]	1170 [930, 1365]	2280 [1980, 2625]	4260 [3600, 5040]	9270 [7260, 12998]	<0.01
Recreational PA (MET-min/week)	570 [0, 1470]	840 [210, 1793]	945 [210, 2130]	1080 [210, 2423]	1260 [176, 2940]	<0.01
Age (years)	69.3 (8.9)	67.6 (8.9)	66.8 (9.4)	65.8 (9.5)	62.2 (9.5)	<0.01
Female	46%	42%	45%	44%	34%	<0.01
Race/ethnicity						<0.01
White	34%	45%	47%	48%	46%	
Chinese	22%	14%	11%	6%	6%	
African-American	22%	22%	24%	28%	26%	
Hispanic	23%	20%	18%	18%	22%	
Level of education						<0.01
< High School	27%	20%	16%	15%	15%	
High School+	31%	30%	36%	37%	41%	
College+	42%	50%	48%	47%	44%	
Annual income						<0.01
<$50,000	71%	62%	61%	61%	62%	
$50,000-$99,999	17%	21%	26%	27%	30%	
$100,000+	12%	17%	13%	12%	8%	
Systolic blood pressure (mm Hg)	132 (22)	132 (22)	131 (22)	131 (22)	128 (20)	<0.01
Hypertension medication	53%	44%	50%	44%	37%	<0.01
Total cholesterol (mg/dL)	193 (37)	191 (34)	194 (37)	195 (36)	199 (38)	<0.01
HDL cholesterol (mg/dL)	49 (14)	50 (14)	50 (14)	50 (15)	48 (15)	0.09
Statin medication	21%	22%	20%	21%	16%	0.04
Cigarette smoking status						0.30
Never	48%	45%	45%	45%	39%	
Former	39%	45%	43%	42%	43%	
Current	12%	10%	12%	13%	17%	
Pack-years of cigarette smoking	0.6 [0, 23]	2.4 [0, 21]	1.4 [0, 24]	0.6 [0, 18]	3.6 [0, 25]	0.13
Diabetes mellitus	21%	14%	17%	14%	14%	<0.01
Body mass index (kg)/(m^2)	27.9 (5.4)	27.9 (5.1)	28.4 (5.3)	28.9 (5.5)	28.7 (5.1)	<0.01

Values presented are means (standard deviations) or medians [interquartile range]. CAC=coronary artery calcium, HDL=high density lipoprotein, MET=metabolic equivalent of task, PA=physical activity.

Table 3: Associations of Recreational and Non-Recreational PA with CAC Density and Volume

Recreational PA	CAC Density				CAC Volume			
	Model 1		*Model 2*		*Model 1*		*Model 2*	
Quintile 1 (ref)	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Quintile 2	0.01	(-.05, .07)	0.01	(-.05, .07)	-0.07	(-.20, .06)	-0.08	(-.21, .05)
Quintile 3	-0.02	(-.08, .04)	-0.03	(-.09, .03)	0.06	(-.07, .19)	0.08	(-.05, .22)
Quintile 4	0.00	(-.06, .06)	-0.02	(-.08, .04)	0.01	(-.13, .14)	0.05	(-.09, .18)
Quintile 5	**0.07**	**(.01, .13)**	0.05	(-.01, .11)	-0.09	(-.22, .05)	-0.02	(-.15, .12)
Quintile 5 vs. 1-4	**0.07**	**(.02, .12)**	**0.06**	**(.01, .11)**	-0.09	(-.19, .02)	-0.03	(-.14, .08)

Non-Recreational PA	CAC Density				CAC Volume			
	Model 1		*Model 2*		*Model 1*		*Model 2*	
Quintile 1 (ref)	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Quintile 2	-0.02	(-.08, .04)	-0.02	(-.08, .04)	0.03	(-.10, .17)	0.07	(-.06, .20)
Quintile 3	-0.04	(-.10, .03)	-0.03	(-.09, .03)	0.10	(-.03, .24)	0.11	(-.03, .24)
Quintile 4	-0.05	(-.12, .01)	-0.06	(-.12, .01)	0.13	(-.01, .26)	**0.16**	**(.03, .30)**
Quintile 5	**-0.08**	**(-.14, -.02)**	**-0.09**	**(-.15, -.02)**	0.13	(-.01, .27)	**0.17**	**(.03, .30)**

Values are regression coefficients and 95% confidence intervals adjusted for recreational and non-recreational PA, CAC density and volume, age, sex, race/ethnicity, annual income, level of education (Model 1) with additional adjustment for CVD risk factors (Model 2, see text). CAC volume is natural log transformed to adjust for skewness. Bolded text indicates $p<0.05$. CAC=coronary artery calcium, PA=physical activity.

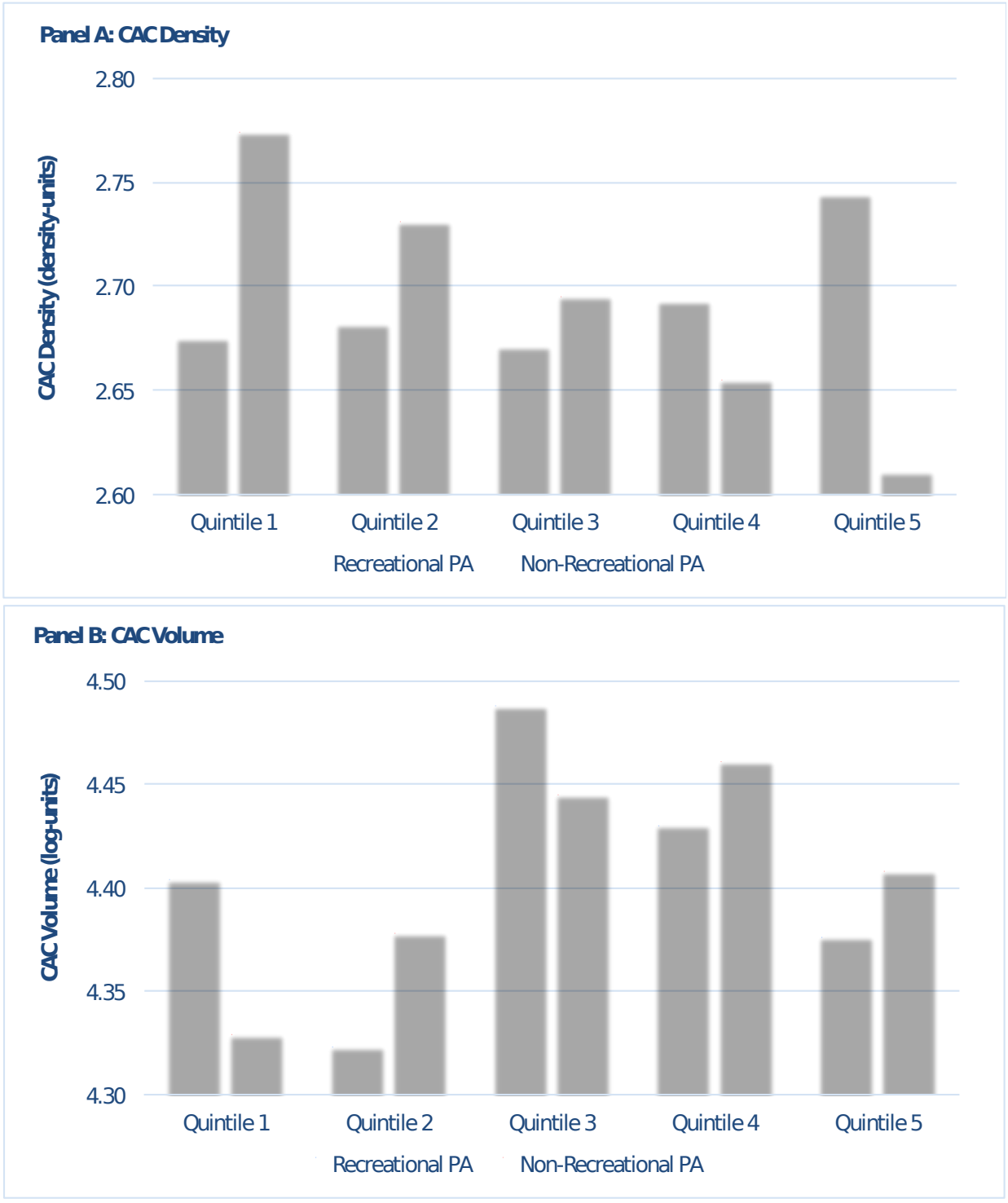
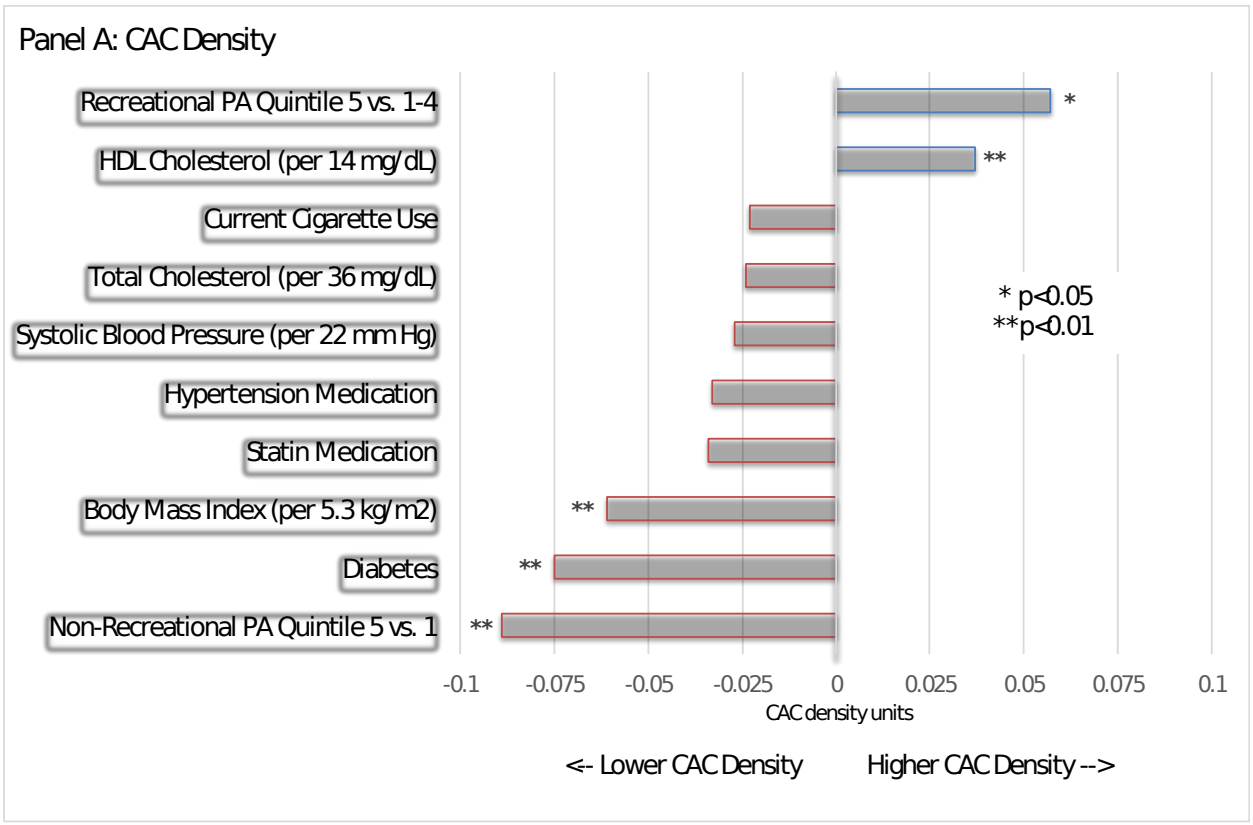


Figure 1: Adjusted mean CAC Density (Panel A) and CAC Volume (Panel B) Across Quintiles of Recreational and Non-recreational PA. Values are mutually-adjusted for Recreational PA, Non-recreational PA, CAC density, and CAC volume. CAC=coronary artery calcium, PA=physical activity.


Panel A: CAC Density
Recreational PA Quintile 5 vs. 1-4
HDL Cholesterol (per 14 mg/dL)
Current Cigarette Use
Total Cholesterol (per 36 mg/dL)
Systolic Blood Pressure (per 22 mm Hg)
Hypertension Medication
Statin Medication
Body Mass Index (per 5.3 kg/m2)
Diabetes
Non-Recreational PA Quintile 5 vs. 1
* p<0.05
**p<0.01
-0.1
-0.075
-0.05
-0.025
0
0.025
0.05
0.075
0.1
CAC density units
<- Lower CAC Density
Higher CAC Density -->

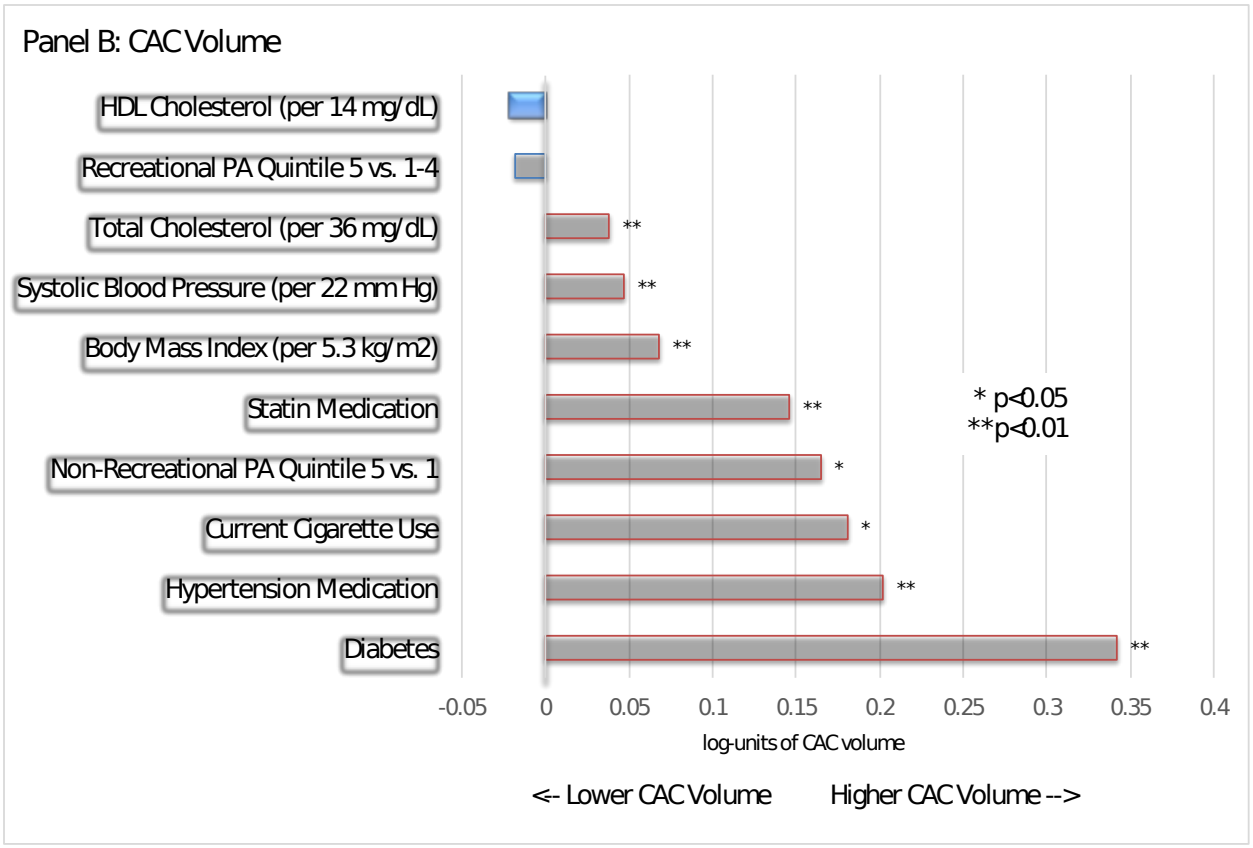

Panel B: CAC Volume
HDL Cholesterol (per 14 mg/dL)
Recreational PA Quintile 5 vs. 1-4
Total Cholesterol (per 36 mg/dL)
Systolic Blood Pressure (per 22 mm Hg)
Body Mass Index (per 5.3 kg/m2)
Statin Medication
Non-Recreational PA Quintile 5 vs. 1
Current Cigarette Use
Hypertension Medication
Diabetes
* p<0.05
**p<0.01
-0.05
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
log-units of CAC volume
<- Lower CAC Volume
Higher CAC Volume -->

Figure 2: Associations of Modifiable CVD Risk Factors with CAC Density (Panel A) and CAC Volume (Panel B). Regression coefficients from the fully-adjusted multiple linear regression model are plotted, with coefficients reflecting one standard deviation increment for continuous variables. Model adjusts for recreational and non-recreational PA, CAC density and volume, demographic and socioeconomic variables, and CVD risk factors (Model 2 in text). CAC=coronary artery calcium, CVD=cardiovascular disease, PA=physical activity.